Docket No. 2307AA-031220US
Client Ref. No. 90-160-5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

STEINUNN BAEKKESKOV et al.

Application No.: 08/838,486

Confirmation No. 8923

Filed: April 7, 1997

For: METHODS FOR THE DIAGNOSIS AND TREATMENT OF DIABETES

Examiner: Gerald R. Ewold

Art Unit: 1644

REPLY BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is submitted in response to the Examiner's Answer mailed March 26, 2006.

1. STATUS OF CLAIMS

Claims 31, 35, 50-57, 59 and 62-67 are pending and rejected. Claims 1-30, 32-34, 36-49, 58, and 60-61 are cancelled. All rejected claims are appealed.

2. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection as modified by the Examiner's answer are as follows:

1. Whether claims 31, 50-53, and 62-67 lack enablement under 35 U.S.C. § 112, first paragraph.

2. Whether claim 31 is anticipated by US 5,762,937 under 35 U.S.C. § 102(e).

3. Whether claims 35 and 54-57 are anticipated by US 5,762,937 under 35 U.S.C. § 102(e).

4. Whether claims 50-53, 59, 66 and 67 would have been obvious under 35 U.S.C. § 103(a) over US 5,762,937.

5. Whether claims 35 and 55-57 would have been obvious under 35 U.S.C. § 103(a) over US 4,086,142 in view of US 4,736,020.

3. ARGUMENT

Issue 1: Claims 31, 50-53, 62-67 are enabled under 35 U.S.C. § 112, first paragraph

At pp. 3-8 of the Examiner's answer, the Examiner essentially repeats the comments from the final rejection. Appellants have already responded to these remarks in the appeal brief and do not further address them here.

At pp. 11-12 of the Examiner's answer, the Examiner reiterates his view that the inhibition of development of disease in a NOD mouse model of disease is not sufficiently predictive of treatment of humans to demonstrate enablement of the present claims. The Examiner dismisses the Baekkeskov declaration's comments in this regard as an opinion. However, the Examiner does not address the evidence on which this opinion was based which included the fact that positive results in the NOD mouse have been used as evidence to support human clinical trials of a number of drugs to treat insulin dependent diabetes mellitus (IDDM, also known as type I diabetes), including humanized OKT3, alpha interferon, and most

importantly GAD (see Baekkeskov declaration at paragraph (6)). The approval of clinical trials shows that the FDA or similar body has found a reasonable basis that the investigation may be successful.

> Before a drug can enter human clinical trials, the sponsor, often the applicant must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary.
>
> MPEP 21707.03.

At p. 13, second paragraph of the Examiner's answer, the Examiner dismisses appellants' comments regarding the significance of phase I trials as mere attorney argument, but fails to address the similar comments in the MPEP quoted above.

The Examiner also alleges that the present case presents an unusual situation under *In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995) in that the claims at issues are directed to methods rather than pharmaceutical compositions. It is respectfully submitted that the present facts and circumstances are not unusual with respect to the patenting of pharmaceuticals or methods of using the same and the rationale of *Brana* is not limited to pharmaceutical compositions. Patent applications directed to either pharmaceutical compositions or methods of treatment are by necessity filed at an early date in this process before public disclosure and long before clinical trials are conducted. For this reason, preclinical evidence, such as animal models, is often relied on to show effectiveness. The Examiner's allegation that the NOD mouse is not sufficiently predictive of success in humans seeks to impose a higher standard than that of the FDA which has permitted clinical trials based on the results in the NOD mouse. Such a position is closely analogous to that by the reversed as "arbitrary and capricious" by the Federal Circuit in *In re Brana,* 34 USPQ2d 1436, 1442.

At pp. 11, 12 and 13 of the Examiner's answer, the Examiner denies that any statistically significant results from a phase II trial of GAD are present in the record, and does not address this evidence. In reply, the results were originally submitted by way of a press

release dated June 14, 2003. The press release was submitted on July 21, 2003, resubmitted December 8, 2006, and entered by the advisory action of April 21, 2005.[1] The background to the trial is further described in the Baekkeskov declaration at paragraph (6). The press release reports that Diamyd™, characterized as a "GAD-vaccine" or "GAD-based vaccine" was safe and achieved a "clear and clear and significant positive effect (p=0.01)" (press release dated June 14, 2003 at p. 1).

Although the Examiner declined to address the press release dated June 14, 2003 in the Examiner's answer, he did comment briefly on it in the advisory action of April 21, 2005. The Examiner dismissed the results as being directed to a small subset of type II diabetes patients, and because in his view it was unclear whether a GAD-based vaccine referred to in the press release actually contained GAD, and because the press release refers to a need to conduct a future studies. In reply, the type of patient selected for the trial (LADA) was discussed in the paragraph bridging pp. 8-9 of the appeal brief. In brief, the patients of this subclass of patients are suffering from autoimmune attack and do have autoantibodies to GAD, as in type I (i.e., IDMM) patients. That a "GAD-based" or "GAD" vaccine means a composition containing GAD as its active ingredient, if not self-evident from the name alone, can be easily inferred from the comments in the penultimate paragraph of p. 1 of the press release. These comments indicate that the vaccine arose from "experiments with diabetes prone-mice that were protected from developing the disease by injecting GAD-protein," and use the term "GAD-vaccine" to describe the GAD-protein injected into mice. Thus, GAD-vaccine means a composition containing GAD protein. Finally, the fact that further studies will be conducted after completion of a successful phase II trial is inherent to the nature of phase II trial and the drug approval process and not an indication of lack of enablement.

In the paragraph bridging pp. 13-14 of the Examiner's answer, the Examiner alleges without citation that the attempted induction of immune tolerance has been the search for the holy grail of autoimmune immunologists for at least two generations. As appellants have previously noted, the issue at hand is the enablement of claims containing a single step of

[1] The Evidence Appendix of the appeal brief gave the date of the advisory action entering the press release as being April 21, 2004 instead of April 21, 2005. The latter date is correct.

administering a therapeutically effective amount of GAD to a patient. Practice of such a method is not dependent on an understanding of the entire field of immunotolerance. It is not disputed by the Examiner that tolerance can be obtained in a NOD mouse model IDDM according to the claimed methods. For the reasons discussed above, it is respectfully submitted that the results in such a model are reasonably predictive of those in humans. Moreover, although further evidence in humans should not be required, the data in mouse have in fact been confirmed by a human clinical trial as discussed above.

At p. 14 of the Examiner's answer, the Examiner states that the term "preventing" in claim 62 most certainly encompasses absolute prevention. Appellants agree that the term preventing encompasses absolute prevention but respectfully submit that the term is not so limited for the reasons identified in the appeal brief. The Examiner has not addressed the explanation provided at p. 11, first paragraph of the appeal brief as to how the claimed methods could achieve absolute prevention of IDDM. Moreover, even assuming *arguendo* that complete prevention was not achievable and that the methods could only inhibit or delay onset of Alzheimer's disease, such would not be inconsistent with enablement. Enabling the full scope of a claim does not necessarily require enabling every embodiment within the claim. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984). This principle is applied to a method of treatment by *In re Cortright*, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999). One of the claims at issue in *In re Cortright* was directed to a method of treating baldness. The Board had rejected the claim for lack of enablement on the basis that the specification did not show restoring the user's hair to its original state (i.e., a full head of hair) but only some improved growth characterized as "filling-in some" or "fuzz" (*Id.* at 1358, 49 USPQ2d at 1467). The Federal Circuit construed the claims as meaning that the claimed method increased the amount of hair grown on the scalp but did not necessarily produce a full head of hair" (*Id.* at 1359, USPQ2d at 1468). The Federal Circuit concluded that the claims, so construed, were enabled, notwithstanding the lack of evidence that complete restoration could be achieved. The same principle is illustrated in a different technology by *CFMT, Inc. v. Yieldup Int'l Corp*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) and *Ex parte Saito*, Appeal No. 2005-1442 (BPAI 2005, nonprecedential opinion).

At p. 15, first paragraph of the Examiner's answer, the Examiner refers to the relatively brief description of therapeutic methods in the present specification. The methods are described in the specification particularly at pp. 19-21. Applicants reiterate that the method is a simple one that recites a single step of administering GAD to a patient. Such a method can be conveyed without voluminous description.

At p. 15 of the Examiner's answer, the Examiner cites *Rasmusson v. SmithKline Beecham Corp* 75 USPQ2d 1297, 1302 (Fed. Cir. 2005) for the proposition that post-filing evidence cannot contribute to enablement of a method. Insofar as *Rasmusson* is asserted to stand for a broad rule that post-filing evidence cannot be used to confirm the teachings of an application, it would be inconsistent with at least two earlier cases from the Federal Circuit or its predecessor, the CCPA. For example, in *In re Brana*, the court stated that postfiling evidence "does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)." 34 USPQ2d 1436, 1441 fn.19 (Fed. Cir. 1995). Similarly, *In re Marzocchi* found that if there was sufficient reason to doubt the specification was in compliance with 35 USC 112, first paragraph, "such a rejection can be overcome by suitable proofs indicating the teaching contained in the specification is truly enabling" (169 USPQ 367, 369 (CCPA 1971)); (see also MPEP § 2164.05: that enablement is determined from the specification as filed "does not preclude the applicant from providing a declaration after the filing date which demonstrates that the claimed invention works"). To the extent there is a conflict between two Federal Circuit panel decisions, the earlier and not the later decision constitutes binding precedent. *Newell Companies v. Kenney Mfg.*, 9 USPQ 1717, 1423 (Fed. Cir. 1988) ("This court has adopted the rule that prior decisions of a panel of the court are binding precedent on subsequent panels unless and until overturned in banc.") Thus, it is respectfully submitted that the rationale of *Rasmusson* should be limited to its particular fact pattern, which is quite different from that here.

In *Rasmusson,* the invention at issue involved use of finasteride to treat prostate cancer. It was apparently known in the art at the priority date that either DHT or testosterone caused prostate cancer and finasteride modulated levels of DHT. The applicant apparently made a lucky guess later proved right that DHT was the relevant molecule. By contrast, in the present

case, it was already known in the art that the 64 kDa pancreatic antigen was the major autoantigen in IDDM (see appeal brief at p. 4, first paragraph), and it was also well known that antigen-induced tolerance could be used to suppress autoimmune disease in several animal models (see Baekkeskov declaration at paragraph (4)). What was missing from the art was a source that would allow purification of the 64 kDa protein in sufficient quantity and purity to use it for therapeutic purposes. The present application provides the missing link by showing the relationship between GAD and the pancreatic 64 kDa antigen, and thus providing an abundant source of protein for use in methods of inducing immunotolerance. The contribution of the present inventors was not a lucky guess between competing theories already in the prior art, but rather a landmark discovery, published in *Nature* (*Nature* 347, 151-156 (September 13, 1990)), and which provided the missing link in prior knowledge to give rise to the presently claimed methods.

For these reasons, it is maintained that the Examiner has not met his burden of proving that successful results obtained in a mouse model (which the Examiner acknowledges is enabled by the specification) are not predictive of similar results in other patients, including humans.

Issue 2: Whether Claim 31 is Anticipated by US 5,762,937 Under 35 U.S.C. § 102(e)

Appellants have requested that this issue be resolved by interference subsequent to this appeal and do not further address the Examiner's remarks regarding this claim.

Issue 3: Claim 54 Not Anticipated by US 5,762,937

At p. 16, last paragraph, the Examiner continues to insist that the lower molecular weight form of GAD is the form of the '937 patent and alleges that it is clearly differentiated from the higher molecular weight 67 kDa form in Example 6. However, the '937 patent contains no reference to lower molecular weight GAD (aka GAD65) or higher molecular weight GAD (aka GAD67) or indication that there are two forms of GAD. Thus, the Examiner's theory appears to be one of inherency; that is, because the lower molecular weight form of GAD is inherently a component of the pancreatic 64 kDa antigen in its native state, an instruction to use

the 64 kDa antigen or GAD for therapy must be construed as in instruction to use the lower molecular weight form of GAD for therapy. The assumption is incorrect because one cannot prepare GAD in 99% purity from the pancreatic 64 kDa antigen in its native state due to the minute amounts of the 64 kDa antigen present and difficulties of purification as discussed at p. 4, 4th paragraph of the appeal brief. Rather, one must look to an alternate source. The '937 patent does not provide clear guidance that would lead one to use 99% pure lower molecular weight GAD from such a source. The '937 patent teaches only that GAD and the 64kDa antigen have homology, not identity (col. 19, lines 49-54). Thus, it was also not apparent from the '937 patent that an instruction to use the 64 kDa antigen must be construed to require the use of GAD at all. Even if it were so construed, there is no reason to construe it to require the use of purified lower molecular weight GAD rather than the higher molecular weight form or a mixture of the two forms. The two forms naturally exist as a mixture in the CNS (see specification at p. 5, lines 26-28) and one would thus naturally purify a mixture of GAD unless taught to do otherwise. The '937 patent does not provide any such teaching. If one sought to purify GAD from cells expressing GAD recombinantly one would obtain whatever form of GAD was being expressed. The '937 patent does not provide any teaching to express the lower molecular weight form of GAD recombinantly. The Examiner has not shown and cannot show that the sequence of GAD provided by the '937 patent (Figs. 1A, B, and C) is the lower molecular weight form.

In sum, the Examiner's theory of inherency is based on a chain of inference to the effect that the skilled person would deduce from the observation of 64 kDa and 67 kDa proteins reactive with IDDM sera (Example 6) in the pancreas that GAD has two corresponding forms, and that the skilled person would also infer that when the '937 patent refers to GAD in general, what is really meant is a reference to the lower molecular weight form of GAD. This chain of inference at best leaves much to the imagination of the skilled person, and does not therefore meet the standard for inherent disclosure, which is that the skilled person would necessarily have prepared lower molecular weight GAD in 99% pure form. "Inherency ... *may not be established by probabilities or possibilities.*" *Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied).

At p. 16, the Examiner attempts to buttress his position regarding the feasibility of purifying lower molecular weight GAD to 99% purity by citing to the teaching of the present specification stating that the protein can be purified by "conventional protein purification techniques." However, the feasibility of such purification depends on the insight provided by the present application and absent from the '937 patent that two forms of GAD exist and a conscious intent to provide the lower molecular weight form in 99% pure form. Without such knowledge and intent, an instruction to use GAD or the 64 kDa pancreatic antigen as a therapeutic agent would not necessarily result in the skilled person producing the lower molecular weight form in 99% pure form but could result in the skilled person producing a mixture of higher or lower molecular forms, or just the higher molecular weight form.

Appellants have requested that the alleged anticipation of claims 35, 49 and 55-57 be determined by interference subsequent to this appeal and do not further address the Examiner's remarks regarding these claims.

Issue 4: Claim 59 Not Obvious Over by US 5,762,937

As discussed in the appeal brief, the nonobviousness of claim 59 over the '937 patent rests on similar grounds to the lack of anticipation of claim 54. Thus, appellants' rebuttal of the Examiner's rationale in connection with claim 54 applies equally to claim 59.

Appellants request obviousness issues with respect to claims 35, 50-53, 66 and 67 be determined by interference.

Issue 5: Claims 35 and 55-57 Not Obvious over US 4,086,142 in view of US 4,732,020

At p. 17 of the Examiner's answer, the Examiner expresses the view that purifying a protein to at least 99% was routine in the art and the '020 patent merely affirms the specification in establishing the desirability of 99% pure proteins. In reply, the Examiner has failed to address appellants' position from p. 15, second paragraph of the appeal brief. An "assertion that one of ordinary skill in the relevant art would have been able to arrive at applicant's invention because he had the necessary skills to carry out the requisite process steps" is an "inappropriate standard for obviousness." *Orthokinetics Inc. vs. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986). The '020 patent may identify the desirability of purifying

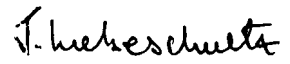
TNF to 99% purity for use as a pharmaceutical. However, neither the '142 patent or '020 patent identifies a pharmaceutical utility for GAD. Reliance on the present specification for such a utility is impermissible. Absent recognition of a therapeutic utility for GAD, the artisan would not have been impelled to impart the teaching of the '020 patent regarding purifying TNF to GAD.

At p. 18 of the Examiner's answer, the Examiner alleges that the present application does not contain any evidence that GAD prepared by any particular technique comprises a different GAD than would be prepared by the purification method of the combined references. These remarks appear to assume that one would have purified GAD from the '142 patent in the same way as one would have prepared TNF from the '020 patent in a form suitable for parenteral administration to a human. However, as discussed above and in the appeal brief (pp. 15-16), absent knowledge that GAD had any therapeutic utility, the skilled person would have had no motivation to have done so.

4. CONCLUSION

For these reasons, as well as the reasons provided in the appeal brief, it is respectfully submitted that the rejections under 35 U.S.C. § 112, should be reversed, as should the rejections under 35 U.S.C. § 102 and § 103 with respect to claims 54 and 59, and the remaining rejection should be remanded to be addressed by interference between the present application and University of Florida, US 6,001,360 and US 5,762,937.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422
61041450 v1

9. EVIDENCE APPENDIX

This appendix lists the references relied on in the appeal brief and/or the reply brief. Copies of references are attached, except for Tisch, *Nature* 355 71-75 (1993) and Harrison, *Molecular Medicine* 1, 722-727 (1994), which were attached to the Examiner's answer.

Baekkeskov declaration including the following attachments (Baekkeskov cv.; Press Release of April 11, 2003; excerpt from *Diabetes Station* downloaded March 6, 2003; Herold, *New. Engl. J. Med.* 346, 1692-1698 (2002) (Abstract); excerpt from *Immune Tolerance News* downloaded March 28, 2003; Golub et al., *The Cellular Basis of the Immune Response*, Second Edition 1981; Cremer et al., *J. Immunol.* 131, 2995-3000 (1983); Scherer et al., *Cold Spring Harbor Symp. Quant. Biol.* 54, 497-50 4 (1989); Nagler-Anderson et al., *Proc. Natl. Acad. Sci. USA* 83, 7443-7446 (1986); Higgins et al., *J. Immunol.* 140, 440-445 (1988)) filed May 20, 2003, and resubmitted July 22, 2003, entered by office action of July 29, 2003.

Kaufman, *Nature* 366, 69-71 (1993), cited in Information Disclosure Statement submitted August 5, 1997, entered by office action of April 28, 1998.

Tisch, Nature 355 71-75 (1993), cited in Information Disclosure Statement submitted August 5, 1997, entered by office action of April 28, 1998.

Tian, *Nature Medicine* 12, 1348 (1996), cited in appellants' communications of October 28, and October 30, 1998, entered by office action of January 22, 1999.

Peterson, *Diabetes* 44, 1478 (1994), cited in appellants' communications of October 28 and October 30, 1998, entered by office action of January 22, 1999.

Harrison, *Molecular Medicine* 1, 722-727 (1994), cited and entered by office action of April 28, 1998.

Benjamini & Leskowitz, *Immunology: A Short Course* (Liss, 1988) at p. 256, cited in communication submitted October 28, 1998, entered by office action of January 22, 1999.

Press Release dated January 17, 2000 attached to response of January 5, 2001, entered by office action of April 24, 2001.

Press Release dated June 14, 2003, filed July 22, 2003, resubmitted December 8, 2004, entered by advisory action of April 21, 2004.

Baekkeskov *et al.*, *Nature* 347, 151-156 (September 13,1990) (#AU on IDS of August 5, 1997 entered by office action of April 28, 1998).